

BREAKING ADVANCES

- 3191 | **Highlights from Recent Cancer Literature**

REVIEWS

- 3193 | **The *MET* Oncogene in Glioblastoma Stem Cells: Implications as a Diagnostic Marker and a Therapeutic Target**
Carla Boccaccio and Paolo M. Comoglio
- 3200 | **Vesicle Trafficking and RNA Transfer Add Complexity and Connectivity to Cell–Cell Communication**
Charles T. Roberts Jr and Peter Kurre

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 3206 | **Application of Raman Spectroscopy to Identify Microcalcifications and Underlying Breast Lesions at Stereotactic Core Needle Biopsy**
Ishan Barman, Narahara Chari Dingari, Anushree Saha, Sasha McGee, Luis H. Galindo, Wendy Liu, Donna Plecha, Nina Klein, Ramachandra Rao Dasari, and Maryann Fitzmaurice
- Précis:* These findings illustrate a powerful noninvasive spectroscopic approach to detect microcalcifications and other cancer-associated lesions that offers real-time feedback to radiologists during biopsy procedures and thus could reduce nondiagnostic and false-negative biopsies.
- 3216 | **Manganese-Enhanced MRI Reveals Early-Phase Radiation-Induced Cell Alterations *In Vivo***
Shigeyoshi Saito, Sumitaka Hasegawa, Aiko Sekita, Rumiana Bakalova, Takako Furukawa, Kenya Murase, Tsuneo Saga, and Ichio Aoki
- Précis:* This study reports a noninvasive method to monitor cell-cycle alterations in tumors based on manganese uptake and MRI, offering a potentially useful tool for longitudinal studies to optimize radiotherapy.

MICROENVIRONMENT AND IMMUNOLOGY

- 3225 | **The Endogenous Tryptophan Metabolite and NAD⁺ Precursor Quinolinic Acid Confers Resistance of Gliomas to Oxidative Stress**
Felix Sahn, Iris Oezen, Christiane A. Opitz, Bernhard Radlwimmer, Andreas von Deimling, Tilman Ahrendt, Seray Adams, Helge B. Bode, Gilles J. Guillemin, Wolfgang Wick, and Michael Platten
- Précis:* A downstream catabolite of the tryptophan degradation pathway of IDO- and TDO-dependent immune escape, which is elevated in the majority of human cancers, is found to be a key element in their therapeutic resistance, with implications to improve treatment.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 3235 | **Hypoxia Triggers Hedgehog-Mediated Tumor–Stromal Interactions in Pancreatic Cancer**
Taly R. Spivak-Kroizman, Galen Hostetter, Richard Posner, Meraj Aziz, Chengcheng Hu, Michael J. Demeure, Daniel Von Hoff, Sunil R. Hingorani, Timothy B. Palculict, Julie Izzo, Galina M. Kiriakova, Mena Abdelmelek, Geoffrey Bartholomeusz, Brian P. James, and Garth Powis
- Précis:* These findings provide evidence for a novel molecular mechanism that explains the high levels of hypoxia and desmoplasia that contribute to therapy resistance in pancreatic cancer.
- 3248 | **Single Copies of Mutant *KRAS* and Mutant *PIK3CA* Cooperate in Immortalized Human Epithelial Cells to Induce Tumor Formation**
Grace M. Wang, Hong Yuen Wong, Hiroyuki Konishi, Brian G. Blair, Abde M. Abukhdeir, John P. Gustin, D. Marc Rosen, Samuel Ray Denmeade, Zeshaan Rasheed, William Matsui, Joseph P. Garay, Morassa Mohseni, Michaela J. Higgins, Justin Cidado, Danijela Jelovac, Sarah Croessmann, Rory L. Cochran, Sivasundaram Karnan, Yuko Konishi, Akinobu Ota, Yoshitaka Hosokawa, Pedram Argani, Josh Lauring, and Ben Ho Park
- Précis:* These findings suggest a paradigm that helps to explain how a single mutant *KRAS* allele can cooperate with mutant *PIK3CA* to impart a transformed phenotype.

3262 **Dachshund Binds p53 to Block the Growth of Lung Adenocarcinoma Cells**

Ke Chen, Kongming Wu, Shaoxin Cai, Wei Zhang, Jie Zhou, Jing Wang, Adam Ertel, Zhiping Li, Hallgeir Rui, Andrew Quong, Michael P. Lisanti, Aydin Tozeren, Ceylan Tanes, Sankar Addya, Michael Gormley, Chenguang Wang, Steven B. McMahon, and Richard G. Pestell

Précis: This report identifies a modifier of EGFR signaling and stem cell function as an important new regulator of p53 in the most common type of lung cancer.

3275 **Lineage Relationship of Gleason Patterns in Gleason Score 7 Prostate Cancer**

Irina V. Kovtun, John C. Cheville, Stephen J. Murphy, Sarah H. Johnson, Shabnam Zarei, Farhad Kosari, William R. Sukov, R. Jeffrey Karnes, and George Vasmatazis

Précis: This work has important clinical implications because it demonstrates that changes associated with aggressive tumor behavior can be identified prior to the morphologic changes characteristic of aggressive prostate cancer.

3285 **Collagen Prolyl Hydroxylases Are Essential for Breast Cancer Metastasis**

Daniele M. Gilkes, Pallavi Chaturvedi, Saumendra Bajpai, Carmen C. Wong, Hong Wei, Stephen Pitcairn, Maimon E. Hubbi, Denis Wirtz, and Gregg L. Semenza

Précis: Although collagen prolyl hydroxylases have been implicated broadly in cancer pathophysiology, their precise contributions have not been well understood, an important gap in knowledge addressed by this study.

3297 **Interleukin-1 β Promotes Skeletal Colonization and Progression of Metastatic Prostate Cancer Cells with Neuroendocrine Features**

Qingxin Liu, Mike R. Russell, Kristina Shahriari, Danielle L. Jernigan, Mercedes I. Lioni, Fernando U. Garcia, and Alessandro Fatatis

Précis: The identification of IL-1 β as an important mediator of metastasis in prostate cancer should prompt immediate testing of anti-IL-1 β strategies to treat advanced disease.

PREVENTION AND EPIDEMIOLOGY

3306 **Colorectal Cancer Risk Associated with Hormone Use Varies by Expression of Estrogen Receptor- β**

Anja Rudolph, Csaba Toth, Michael Hoffmeister, Wilfried Roth, Esther Herpel, Peter Schirmacher, Hermann Brenner, and Jenny Chang-Claude

Précis: Expression of estrogen receptor β , the predominant estrogen receptor in colon tissue, appears to be involved in the reduction of colorectal cancer risk that may arise with use of oral contraceptives or menopausal hormone therapy.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

3316 **Inhibition of Tumor Cell Migration by LD22-4, an N-Terminal Fragment of 24-kDa FGF2, Is Mediated by Neuropilin 1**

Ling Zhang, Graham C. Parry, and Eugene G. Levin

Précis: Definition of a cell surface receptor for an inhibitor of cancer cell migration suggests a novel approach to tumor suppression.

3326 **DNA Methylation-Mediated Repression of miR-886-3p Predicts Poor Outcome of Human Small Cell Lung Cancer**

Jianzhong Cao, Yongmei Song, Nan Bi, Jie Shen, Wenyang Liu, Jing Fan, Guogui Sun, Tong Tong, Jie He, Yuankai Shi, Xun Zhang, Ning Lu, Yinghua He, Hongyu Zhang, Kelong Ma, Xiaoying Luo, Lei Lv, Hui Deng, Jing Cheng, Jingde Zhu, Luhua Wang, and Qimin Zhan

Précis: These findings identify a little-studied microRNA the epigenetic downregulation of which strongly affects clinical outcomes and malignant cell behaviors in small-cell lung cancer.

3336 **PFI-1, a Highly Selective Protein Interaction Inhibitor, Targeting BET Bromodomains**

Sarah Picaud, David Da Costa, Angeliki Thanasopoulou, Panagis Filippakopoulos, Paul V. Fish, Martin Philpott, Oleg Fedorov, Paul Brennan, Mark E. Bunnage, Dafydd R. Owen, James E. Bradner, Philippe Taniere, Brendan O'Sullivan, Susanne Müller, Juerg Schwaller, Tatjana Stankovic, and Stefan Knapp

Précis: This study suggests that it may be possible to target an important transcriptional regulatory domain that has been implicated in a broad number of aggressive blood cancers, as a generalizable therapeutic approach.

3347 **Bevacizumab-Induced Normalization of Blood Vessels in Tumors Hampers Antibody Uptake**

Marlous Arjaans, Thijs H. Oude Munnink, Sjoukje F. Oosting, Anton G.T. Terwisscha van Scheltinga, Jourik A. Gietema, Erik T. Garbacik, Hetty Timmer-Bosscha, Marjolijn N. Lub-de Hooge, Carolina P. Schröder, and Elisabeth G.E. de Vries

Précis: Bevacizumab treatment decreases tumor uptake of antibodies by vessel normalization, and this should be taken into account in the design of clinical trials that combine bevacizumab with other antibodies.

3356

Threshold Levels of ABL Tyrosine Kinase Inhibitors Retained in Chronic Myeloid Leukemia Cells Determine Their Commitment to Apoptosis

Thomas O'Hare, Christopher A. Eide, Anupriya Agarwal, Lauren T. Adrian, Matthew S. Zabriskie, Ryan J. MacKenzie, Dorian H. LaTocha, Kara J. Johnson, Huihong You, Jenny Luo, Steven M. Riddle, Bryan D. Marks, Kurt W. Vogel, Dennis R. Koop, John Apgar, Jeffrey W. Tynner, Michael W. Deininger, and Brian J. Druker

Précis: By providing deeper insights into the pharmacodynamic requirements for the cytotoxic effects of the paradigm kinase inhibitor imatinib, this study may more broadly assist the development of maximally effective kinase inhibitors for cancer treatment.

3371

Simultaneous Targeting of Tumor Antigens and the Tumor Vasculature Using T Lymphocyte Transfer Synergize to Induce Regression of Established Tumors in Mice

Dhanalakshmi Chinnasamy, Eric Tran, Zhiya Yu, Richard A. Morgan, Nicholas P. Restifo, and Steven A. Rosenberg

Précis: This study offers proof of principle for using antiangiogenic drugs to enhance the efficacy of adoptive T-cell therapies for cancer treatment.

3381

Hedgehog Signaling Alters Reliance on EGF Receptor Signaling and Mediates Anti-EGFR Therapeutic Resistance in Head and Neck Cancer

Stephen B. Keysar, Phuong N. Le, Ryan T. Anderson, J. Jason Morton, Daniel W. Bowles, Jeremiah J. Paylor, Brian W. Vogler, Jackie Thorburn, Pamela Fernandez, Magdalena J. Glogowska, Sarah M. Takimoto, Daniel B. Sehart, Gregory N. Gan, Justin R. Eagles-Soukup, Hilary Serracino, Fred R. Hirsch, M. Scott Lucia, Andrew Thorburn, John I. Song, Xiao-Jing Wang, and Antonio Jimeno

Précis: Preclinical results show that resistance to the widely used EGFR targeting drug cetuximab, which occurs widely in the clinic, could be prevented by administration of inhibitors of the hedgehog pathway, which appears to be emerging as a major factor in cancer drug resistance more broadly.

3393

Regulation of FANCD2 by the mTOR Pathway Contributes to the Resistance of Cancer Cells to DNA Double-Strand Breaks

Changxian Shen, Duane Oswald, Doris Phelps, Hakan Cam, Christopher E. Pelloski, Qishen Pang, and Peter J. Houghton

Précis: This study provides the basis for the sensitization of cancer cells to DNA damaging agents by targeting the mTOR pathway and gives insight into potential strategies that may enhance therapeutic activity or reduce sequelae from high-dose therapies, particularly in children.

3402

Elevation of Receptor Tyrosine Kinases by Small Molecule AKT Inhibitors in Prostate Cancer Is Mediated by Pim-1

Bo Cen, Sandeep Mahajan, Wenxue Wang, and Andrew S. Kraft

Précis: This study provides a rationale to improve the efficacy of AKT inhibitors for cancer therapy.

TUMOR AND STEM CELL BIOLOGY

3412

CIP4 Controls CCL19-Driven Cell Steering and Chemotaxis in Chronic Lymphocytic Leukemia

Gema Malet-Engra, Julien Viaud, Loïc Ysebaert, Manon Farcé, Fanny Lafouresse, Guy Laurent, Frédérique Gaits-Iacovoni, Giorgio Scita, and Loïc Dupré

Précis: This study offers important new mechanistic insights into how leukemia cells migrate, with potentially important implications for understanding how to block invasive growth by these cells.

3425

miR145 Targets the SOX9/ADAM17 Axis to Inhibit Tumor-Initiating Cells and IL-6-Mediated Paracrine Effects in Head and Neck Cancer

Cheng-Chia Yu, Lo-Lin Tsai, Mong-Lien Wang, Chuan-Hang Yu, Wen-Liang Lo, Yun-Ching Chang, Guang-Yuh Chiou, Ming-Yung Chou, and Shih-Hwa Chiou

Précis: This mechanistically extensive study reveals a core pathway of support for cancer stem-like cells in head and neck squamous carcinomas, with implications for new treatment strategies in this setting.

3441

Cytomegalovirus Contributes to Glioblastoma in the Context of Tumor Suppressor Mutations

Richard L. Price, Jieun Song, Katherine Bingmer, Tae Hyong Kim, Ji-Yeun Yi, Michal O. Nowicki, Xiaokui Mo, Todd Hollon, Eric Murnan, Christopher Alvarez-Breckenridge, Soledad Fernandez, Balveen Kaur, Andreeana Rivera, Michael Oglesbee, Charles Cook, E. Antonio Chiocca, and Chang-Hyuk Kwon

Précis: A virus that infects a large proportion of humans is linked for the first time to formation of brain tumors in a mouse model.

3451

Notch3 Functions as a Tumor Suppressor by Controlling Cellular Senescence

Hang Cui, Yahui Kong, Mei Xu, and Hong Zhang

Précis: These findings offer a novel mechanism to enhance our understanding of the tumor-suppressive function of Notch signaling in cancer, with implications in many solid tumor settings.

3460

Dual Role of the Antioxidant Enzyme Peroxiredoxin 6 in Skin Carcinogenesis

Frank Rolfs, Marcel Huber, Florian Gruber, Friederike Böhm, Herbert J. Pfister, Valery N. Bochkov, Erwin Tschachler, Reinhard Dummer, Daniel Hohl, Matthias Schäfer, and Sabine Werner

Précis: Antioxidant functions do not contribute exclusively to tumor suppression, as widely believed, but can also promote tumor development depending on the stage of the disease.

3470

Growth of Triple-Negative Breast Cancer Cells Relies upon Coordinate Autocrine Expression of the Proinflammatory Cytokines IL-6 and IL-8

Zachary C. Hartman, Graham M. Poage, Petra den Hollander, Anna Tsimelzon, Jamal Hill, Nattapon Panupinthu, Yun Zhang, Abhijit Mazumdar, Susan G. Hilsenbeck, Gordon B. Mills, and Powel H. Brown

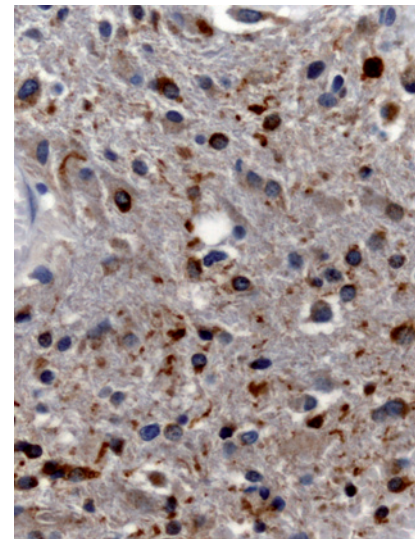
Précis: Findings offer a preclinical proof of principle to improve therapy of triple-negative breast cancer, a particularly aggressive disease subtype lacking effective mechanism-based interventions.

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ABOUT THE COVER

In gliomas, constitutive metabolism of the essential amino acid tryptophan leads to the accumulation of the tryptophan metabolite quinolinic acid. Quinolinic acid is used by tumor cells to generate NAD⁺, thus contributing to the resistance towards radiotherapy and chemotherapy by replenishing depleted intracellular NAD pools. Using Western blot analyses and immunohistochemistry, it was found that the key enzyme leading to accumulation of quinolinic acid, 3-hydroxyanthranilate oxygenase (3-HAO), is expressed by tumor-infiltrating monocytes. Thus, infiltrating monocytes contribute to resistance to cytotoxic therapies in malignant gliomas. For details, see article by Sahm and colleagues on page 3225.



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